APPENDIX

Copy of a "Second Declaration of Dr. Malcolm John Stoker Pursuant to 37 CFR § 1.132," dated June 18, 2007.

PATENT

IN THE UNITED STATES PATENT
AND TRADEMARK OFFICE

Applicants:	Erik H.F. Wong et al.
Serial No.:	10/758,864
Filed:	January 16, 2004
Title:	METHOD OF TREATING PERIPHERAL NEUROPATHY
Group Art Unit:	1614
Examiner:	Brian Yong S. Kwon
Attorney Docket No.:	30744/6248.11

SECOND DECLARATION OF DR. MALCOLM JOHN STOKER PURSUANT TO 37 CFR §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

1. I am the same Malcolm John Stoker that previously executed a declaration ("Declaration of Dr. Malcolm John Stoker Pursuant To 37 CFR §1.132," dated July 31, 2006), hereinafter referred to as the "2006 Stoker declaration," that I am informed was submitted to the U.S. Patent and Trademark Office ("Patent Office") in connection with the above-captioned patent application.

2. I have reviewed the application and am familiar with the subject matter disclosed therein.

3. I have reviewed and am familiar with a Patent Office action dated January 18, 2007, in which the Patent Office commented on the application.

4. On March 21, 2007, I participated in an interview at the Patent Office with an attorney prosecuting this application (Sandip H. Patel), one of my colleagues (Keith S. Ruddock), and the examiner responsible for reviewing the application (Brian Yong S. Kwon).

5. My education and professional experience have been accurately described in paragraphs 4 and 5 of the 2006 Stoker declaration.

6. Based on the foregoing, I am qualified to provide the comments set forth herein regarding the subject matter of the application.

7. The 2006 Stoker declaration (¶ 7) represented that peripheral neuropathy "is art-recognized and diagnosed as a 'symptom complex' rather than a disease entity," and treatment of a symptom complex may be accomplished by alleviating or otherwise controlling one or more symptoms. Pain is a known major symptom of peripheral neuropathy requiring treatment.

8. The 2006 Stoker declaration (¶ 8) also represented that diabetic peripheral neuropathy (DPN) and post herpetic neuralgia (PHN) are major types of peripheral neuropathy characterized by the representative neuropathic pain symptoms requiring treatment.

9. The 2006 Stoker declaration (¶s 12-16) additionally represented that Pfizer Study Protocol A6061001 demonstrated in a Phase II clinical trial that (S,S) reboxetine provided effective relief to patients suffering from chronic pain associated with PHN that had failed to respond to gabapentin treatment. *See, e.g.*, the Ratcliffe declaration, referred to therein, at p. 1, ¶ 7 (stating that she "consider[s] that ssRBX [(S,S) reboxetine] is associated with an unexpected[ly] lower tachycardia adverse event frequency in chronic pain patients with post-herpetic neuralgia (PHN)); and at p. 12 (Appendix 5) (stating that "ssRBX [(S,S) reboxetine] was clearly efficacious in the treatment of PHN in subjects who are GBP [gabapentin] treatment failures").

10. The 2006 Stoker declaration (¶ 17) stated that, because PHN is a representative disorder to study when considering the effective treatment of painful peripheral neuropathy, it is reasonable to conclude that (S,S) reboxetine would be effective in the general treatment of painful peripheral neuropathy. Such a conclusion is further supported by the representations set out below.

11. As a result of the finding in the application that (S,S) reboxetine is a highly selective norepinephrine reuptake inhibitor and may be useful for the treatment of chronic pain associated with peripheral neuropathy, a neuroanatomical rationale for the efficacy of (S,S) reboxetine in the treatment of painful peripheral neuropathy in general can now be provided as follows.

    (a) Norepinephrine transporters (NETs) provide the primary mechanism whereby the action of norepinephrine at the noradrenergic synapse is terminated.

    (b) Consequently, inhibitors of NET lead to enhanced noradrenergic transmission.

(c) Investigations using neuronal lesions in the periphery and brain support a localization of NETs to innervating, noradrenergic terminals rather than target cells.

(d) An inhibitory, descending noradrenergic pathway, from the nuclei of the brainstem and mid-brain that terminates on neurons of the dorsal horn, is thought to play a role in pain transmission (see Melzack et al, "Pain Mechanisms: A new theory", Science, 1965;150:971-79).

(e) Enhancing descending noradrenergic transmission to the spinal cord is therefore expected to decrease the transmission of painful stimuli to the brain through inhibitory actions at the superficial laminae of the dorsal horn of the spinal cord.

(f) Selective norepinephrine reuptake inhibition by (S,S) reboxetine is thus expected to provide effective pain relief for the treatment of chronic pain associated with peripheral neuropathy, such as painful neuropathy in patients with diabetes mellitus, post herpetic neuralgia, and chronic pain associated with other forms of peripheral neuropathy.

12. This expectation is further supported by the results obtained from pre-clinical, *in vivo*, proof-of-concept experiments, which were performed with (S,S) reboxetine to treat neuropathic pain in three well-established animal models. These models are as follows:

(a) Chung (rat) model;

(b) Bennett (rat) model; and,

(c) Diabetic streptozocin mouse model.

13. Two of these pre-clinical animal models involve the induction of traumatic nerve injury and are widely used to screen potential drugs for efficacy in treating pain associated with peripheral neuropathies of diverse origin:

(a) The Chung (rat) model involves ligation of the L5 & L6 (rat) nerve roots.

(b) The Bennett (rat) model involves chronic constriction injury to the (rat) sciatic nerve.

In both of these models, the surgical procedures (chronic constriction injury (CCI) and spinal nerve ligation (SNL)) cause tactile allodynia. Tactile allodynia is a painful response to non-noxious, mechanical stimulation, frequently present in human chronic pain syndromes where, for example, the afflicted individual may perceive pain

from light pressure or the movement of clothes over the skin. Tactile allodynia is measured by stimulating an affected area with a filament that delivers a graded force and recording the force required to elicit a painful response. In the models discussed, nerve injury was produced in rats by chronic constriction injury (CCI) of the sciatic nerve in accordance with published procedures[1] or by tight ligation of the L5 and L6 spinal nerves (SNL) also in accordance with published procedures[2]. Tactile allodynia was measured eight days later[3] as the force withstood by the affected paw (until paw withdrawal). Normal or sham animals tolerate 15 grams of force, which tolerance was used as a cutoff.

14. A third pre-clinical animal model (model (c) in ¶ 12, supra) involves the induction of diabetes in mice via administration of streptozocin. This third model is predictive for the efficacy of treating pain in patients with diabetic peripheral neuropathy (DPN). Chemically induced diabetes in rodents causes tactile allodynia and thermal hyperalgesia.[4] Thermal hyperalgesia is an exaggerated response to heat pain and may be considered to be analogous to human DPN. Thermal hyperalgesia is measured by the time for an animal to withdraw the hind paw on the nerve-injured side from a heat source. In this model, diabetes induced in mice by injection of streptozocin was monitored by the rise in blood glucose concentrations. Studies were performed at predetermined optimal times and maximally effective doses of test compounds.

15. Pharmacokinetic studies conducted in-house demonstrate the low bioavailability of orally administered reboxetine enantiomers in rats and mice. According to these studies, the bioavailability of 5 mg/kg (S,S) reboxetine in rats was 1% when orally administered, 30% when administered intraperitoneally (IP), and 83% when administered subcutaneously (SC). Accordingly, parenteral (IP) administration was used in the efficacy models to circumvent the low oral bioavailability of reboxetine enantiomers in rodents. After a 5 mg/kg IP dose of (S,S) reboxetine, the AUC was 335 ng·h/mL. At this dose, based on an unbound fraction of 17% in rats, the calculated AUC of 57 ng·h/mL for unbound (S,S) reboxetine was comparable to the

---

[1] GJ Bennett and YK Xie (1988) *Pain* **33**:87-107.

[2] SH Kim and JM Chung (1992) *Pain* **50**:355-63

[3] SR Chaplan *et al.* (1993) *J. Neurosci Methods* **53**:55-63.

[4] A Fox *et al.* (1999); *Pain* **81**:307-16; NA Calcutt *et al.* (1997) *Brit. J. Pharmacol.* **122**:267-74.

AUC of 43 ng·h/mL for unbound (S,S) reboxetine in humans receiving 4 mg/kg doses of racemic reboxetine twice daily (BID).

16. The results obtained in these models (models (a) through (c) in ¶ 12, supra) of neuropathic pain are summarized in the appended Table (Appendix 1) and are discussed below. These results support the rationale that (S,S) reboxetine may be used for the treatment of painful peripheral neuropathy in general, and leads to the prediction that (S,S) reboxetine will be useful to treat a patient suffering from chronic pain associated with peripheral neuropathy.

(i) The IP dose-response study in the rat CCI model (model (b) in ¶ 12, supra) compared (S,S) reboxetine with amitriptyline and gabapentin, drugs known to be effective in experimental studies of chronic pain associated with peripheral neuropathy. (S,S) reboxetine and gabapentin were effective in this model (and amitriptyline induced variable results). The results are reported in the appended Table under Study "i."

(ii) In a further study in this rat CCI model, (S,S) reboxetine induced reversal of tactile allodynia as did gabapentin and nortriptyline—drugs known to be effective in experimental studies of chronic pain associated with peripheral neuropathy— further indicating the efficacy of (S,S) reboxetine in this peripheral neuropathy model. The results are reported in the appended Table under Study "ii."

(iii) In the study in the rat SNL model (model (a) in ¶ 12, supra), sub-cutaneous (sc) administration of (S,S) reboxetine was shown to have efficacy that was dose and time dependent. The results are reported in the appended Table under Study "iii," and also show that (S,S) reboxetine is the more active enantiomer in this painful peripheral neuropathy model. Specifically, at doses of 1 to 20 mg/kg, (S,S) reboxetine induced complete reversal of pain resulting from tactile allodynia, whereas (R,R) reboxetine was ineffective.

(iv) In another study performed in mice having diabetic peripheral neuropathy (model (c) in ¶ 12, supra), (S,S) reboxetine demonstrated efficacy in relieving thermal hyperalgesia as did gabapentin and amitriptyline. The results are reported in the appended Table under Study "iv."

17. The efficacy results obtained from the foregoing pre-clinical studies further support the conclusion in the 2006 Stoker declaration (a conclusion supported by the efficacy data Pfizer obtained in its clinical study of the treatment of patients suffering from chronic pain associated with PHN (a representative peripheral neuropathy)) that it is reasonable to conclude that (S,S) reboxetine would be effective in the treatment of chronic pain associated with peripheral neuropathy in general.

18. Pfizer has initiated additional clinical studies for (S,S) reboxetine since completing Pfizer Study Protocol A6061001. Specifically, Pfizer has initiated a long-term open label study (Pfizer Study Protocol A6061031) (see ClinicalTrials.gov Identifier NCT00348894 attached as Appendix 2) in patients with painful diabetic peripheral neuropathy (DPN). At the assessment point of 1st April, 2007, 36 patients had been treated with (S,S) reboxetine in this study. An interim evaluation of the efficacy data from this study indicates an evolving pain response with time with those patients on (S,S) reboxetine. This is illustrated in the Figure appended hereto as Appendix 3. This interim study result indicates that (S,S) reboxetine is efficacious in the treatment of painful DPN.

19. This interim evaluation in this on-going clinical study (Pfizer Study Protocol A6061031), coupled with the results of the aforementioned Pfizer Study Protocol A6061001, support the efficacy of (S,S) reboxetine in treating chronic pain arising from two representative peripheral neuropathies, i.e., DPN and PHN.

20. Given the efficacy demonstrated by (S,S) reboxetine in a range of preclinical studies predictive of efficacy in the treatment of painful peripheral neuropathy, and the efficacy shown in completed or on-going clinical studies involving patients suffering from chronic pain associated with PHN and DPN, it is reasonable to conclude that (S,S) reboxetine would be effective to treat a patient suffering from chronic pain associated with peripheral neuropathy.

21. All statements made herein are of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under 18 USC § 1001 and may jeopardize the validity of the application or any patent which may issue thereon.

Declared at Sandwich in the county of Kent in England this 18th day of June 2007, by

M. J. Stoker

Malcolm John Stoker

before me

Notary Public

My commission expires with life.

Andrew Martin Johnson B.A.
NOTARY PUBLIC
29 St. George's Place
Canterbury
CT1 1UT, England
Tel: 01227 479479

APPENDIX 1

Table

Study	Drug	Route	Dose (mg/kg)	Effect
	Model (b): Tactile Allodynia in Rat CCI Model			
i	(S,S) Reboxetine	IP	1 - 20	Up to 29% dose related reversal ($p<0.05$)
	Amitriptyline	IP	3 - 30	Variable efficacy (ns)
	Gabapentin	IP	10 - 100	Up to 61% dose related reversal ($p<0.05$)
ii	(S,S) Reboxetine	IP	30	48% reversal ($p<0.05$)
	Nortriptyline	IP	30	28% reversal (ns)
	Gabapentin	IP	30	62% reversal ($p<0.05$)
	Model (a): Tactile Allodynia in Rat SNL Model			
iii	(S,S) Reboxetine	SC	5 -20	Dose and time dependent reversal; complete reversal up to 6 hours at 20 mg/kg
	(S,S) Reboxetine	SC	1 - 20	Up to 91% dose related reversal ($p<0.05$)
	(R,R) Reboxetine	SC	1 - 20	No significant effect
	Model (c): Thermal Hyperalgesia in Diabetic Mice			
iv	(S,S) Reboxetine	IP	1 - 20	Complete reversal at 20 mg/kg
	Amitriptyline	IP	0.5 - 10	Approx 60% reversal at 10 mg/kg
	Gabapentin	IP	1 - 100	Complete reversal at 100 mg/kg

CCI=chronic constriction injury; ns=not statistically significant; SNL = spinal nerve ligation

M. J. Stoker

Andrew Martin Johnson B.A.
NOTARY PUBLIC
29 St. George's Place
Canterbury
CT1 1UT, England
Tel: 01227 479479

APPENDIX 2

M. J. Stoker

Andrew Martin Johnson B.A.
NOTARY PUBLIC
29 St. George
Cardiff
CT1 1
Tel: 01222

[S,S]-Reboxetine Long Term Safety Study In Chronic Painful Diabetic Peripheral Neuropathy.

This study is currently recruiting patients.
Verified by Pfizer June 2007

Sponsored by: Pfizer
Information provided by: Pfizer
ClinicalTrials.gov Identifier: NCT00348894

Purpose

The purpose of this study is to assess the long-term safety and tolerability of [S,S]-Reboxetine in patients with chronic painful diabetic peripheral neuropathy

Condition	Intervention	Phase
Pain	Drug: [S,S]-Reboxetine	Phase II

MedlinePlus related topics: Pain

Study Type: Interventional
Study Design: Treatment, Randomized, Open Label, Active Control, Parallel Assignment, Safety/Efficacy Study

Official Title: A Phase 2b Long-Term, Randomized, Open-Label, Safety And Tolerability Trial Comparing [S,S]-Reboxetine (PNU-165442g) With Routine Care In Patients With Chronic Painful Diabetic Peripheral Neuropathy (DPN).

Further study details as provided by Pfizer:
Primary Outcome Measures:

- Vital signs
- Physical examination
- 12-lead ECG
- Hematology/Biochemistry
- Adverse events

Secondary Outcome Measures:

- Pain Visual Analogue Scale
- Patient Global Impression of Change
- Neuropathic Pain Symptom Inventory
- Modified Brief Pain Inventory-Short Form
- SF-12 Health Survey
- EQ-5D

- Analgesic Treatment Satisfaction Scale
- Pain-related Medication Utilization

Total Enrollment: 800

Study start: July 2006

Eligibility

Ages Eligible for Study: 18 Years and above, Genders Eligible for Study: Both

Criteria

Inclusion Criteria:

- Diagnosis of type 1 or 2 diabetes mellitus, with painful, distal, symmetrical, sensorimotor polyneuropathy
- Patients at screening must have a score >/=40 mm on the pain visual analogue scale

Exclusion Criteria:

- Patients with significant hepatic impairment
- Patients with other severe pain, that may impair the self-assessment of the pain due to DPN

Location and Contact Information

Please refer to this study by ClinicalTrials.gov identifier NCT00348894

Pfizer CTgov Call Center 1-800-718-1021

United States, Arizona
Pfizer Investigational Site, Phoenix, Arizona, United States; Recruiting

United States, Arkansas
Pfizer Investigational Site, Jonesboro, Arkansas, United States; Recruiting

United States, California
Pfizer Investigational Site, Huntington Beach, California, United States; Recruiting

Pfizer Investigational Site, Auburn, California, United States; Recruiting

Pfizer Investigational Site, Orangevale, California, United States; Recruiting

United States, Florida
Pfizer Investigational Site, Winter Park, Florida, United States; Recruiting

Pfizer Investigational Site, Naples, Florida, United States; Not yet recruiting

United States, Hawaii
Pfizer Investigational Site, Honululu, Hawaii, United States; Recruiting

ıited States, Illinois
Pfizer Investigational Site, Chicago, Illinois, United States; Recruiting

United States, Missouri
Pfizer Investigational Site, Jefferson City, Missouri, United States; Recruiting

Pfizer Investigational Site, St Louis, Missouri, United States; Not yet recruiting

Pfizer Investigational Site, St. Louis, Missouri, United States; Not yet recruiting

United States, Nebraska
Pfizer Investigational Site, Omaha, Nebraska, United States; Not yet recruiting

United States, Nevada
Pfizer Investigational Site, Las Vegas, Nevada, United States; Recruiting

Pfizer Investigational Site, Reno, Nevada, United States; Not yet recruiting

United States, New Hampshire
Pfizer Investigational Site, Nashua, New Hampshire, United States; Not yet recruiting

United States, New York
Pfizer Investigational Site, Syracuse, New York, United States; Recruiting

United States, North Carolina
Pfizer Investigational Site, Greensboro, North Carolina, United States; Not yet recruiting

United States, Texas
Pfizer Investigational Site, Dallas, Texas, United States; Recruiting

United States, Virginia
Pfizer Investigational Site, Richmond, Virginia, United States; Recruiting

United States, Washington
Pfizer Investigational Site, Tacoma, Washington, United States; Not yet recruiting

Argentina
Pfizer Investigational Site, Buenos Aires, Argentina; Recruiting

Canada, Manitoba
Pfizer Investigational Site, Winnipeg, Manitoba, Canada; Recruiting

Canada, Ontario
Pfizer Investigational Site, Toronto, Ontario, Canada; Recruiting

Pfizer Investigational Site, Ottawa, Ontario, Canada; Recruiting

Canada, Quebec
Pfizer Investigational Site, Laval, Quebec, Canada; Recruiting

Pfizer Investigational Site, Montreal, Quebec, Canada; Recruiting

Estonia
Pfizer Investigational Site, Tallinn, Estonia; Recruiting

Pfizer Investigational Site, Pärnu, Estonia; Recruiting

Pfizer Investigational Site, Viljandi mk., Estonia; Recruiting

Pfizer Investigational Site, Tartu, Estonia; Recruiting

Finland

Pfizer Investigational Site, Tampere, Finland; Recruiting

Pfizer Investigational Site, Seinajoki, Finland; Recruiting

Pfizer Investigational Site, Oulu, Finland; Recruiting

Pfizer Investigational Site, Helsinki, Finland; Recruiting

Germany

Pfizer Investigational Site, Meissen, Germany; Not yet recruiting

Pfizer Investigational Site, St.Ingbert, Germany; Not yet recruiting

Pfizer Investigational Site, Wuerzburg, Germany; Recruiting

Pfizer Investigational Site, Mainz, Germany; Not yet recruiting

Pfizer Investigational Site, Tann i.d. Rhoen, Germany; Recruiting

Pfizer Investigational Site, Muenster, Germany; Recruiting

Pfizer Investigational Site, Bad Mergentheim, Germany; Recruiting

India

Pfizer Investigational Site, Vellore, India; Recruiting

Pfizer Investigational Site, Ludhiana, India; Recruiting

India, Andhra Pradesh

Pfizer Investigational Site, Hyderabad, Andhra Pradesh, India; Recruiting

India, Karnataka

Pfizer Investigational Site, Bangalore, Karnataka, India; Recruiting

India, MUMBAI

Pfizer Investigational Site, Maharashtra, MUMBAI, India; Recruiting

Poland

Pfizer Investigational Site, Wroclaw, Poland; Recruiting

Pfizer Investigational Site, Otwock, Poland; Recruiting

Pfizer Investigational Site, Lublin, Poland; Recruiting

Pfizer Investigational Site, Lodz, Poland; Recruiting

Pfizer Investigational Site, Lask, Poland; Recruiting

ussian Federation
Pfizer Investigational Site, St. Petersburg, Russian Federation; Recruiting

Pfizer Investigational Site, Moscow, Russian Federation; Recruiting

South Africa
Pfizer Investigational Site, Durban, South Africa; Recruiting

Pfizer Investigational Site, Pretoria, South Africa; Recruiting

Pfizer Investigational Site, Soweto, South Africa; Recruiting

Pfizer Investigational Site, Houghton, Johannesburg, South Africa; Recruiting

South Africa, Gauteng Province
Pfizer Investigational Site, Parktown, Gauteng Province, South Africa; Recruiting

Pfizer Investigational Site, Johannesburg, Gauteng Province, South Africa; Recruiting

South Africa, Overport
Pfizer Investigational Site, Durban, Overport, South Africa; Recruiting

Sweden
Pfizer Investigational Site, Göteborg, Sweden; Recruiting

Pfizer Investigational Site, Göteborg, Sweden; Not yet recruiting

Pfizer Investigational Site, GOTEBORG, Sweden; Recruiting

Ukraine
Pfizer Investigational Site, Kyiv, Ukraine; Recruiting

Pfizer Investigational Site, Donetsk, Ukraine; Recruiting

Pfizer Investigational Site, Kharkiv, Ukraine; Recruiting

Pfizer Investigational Site, Dnipropetrovsk, Ukraine; Not yet recruiting

Pfizer Investigational Site, Odessa, Ukraine; Recruiting

United Kingdom
Pfizer Investigational Site, London, United Kingdom; Not yet recruiting

Pfizer Investigational Site, Dundee, United Kingdom; Recruiting

Pfizer Investigational Site, Bath, United Kingdom; Recruiting

United Kingdom, Surrey
Pfizer Investigational Site, Carshalton, Surrey, United Kingdom; Not yet recruiting

Study chairs or principal investigators

Pfizer CT.gov Call Center, Study Director, Pfizer

More Information

To obtain contact information for a study center near you, click here.

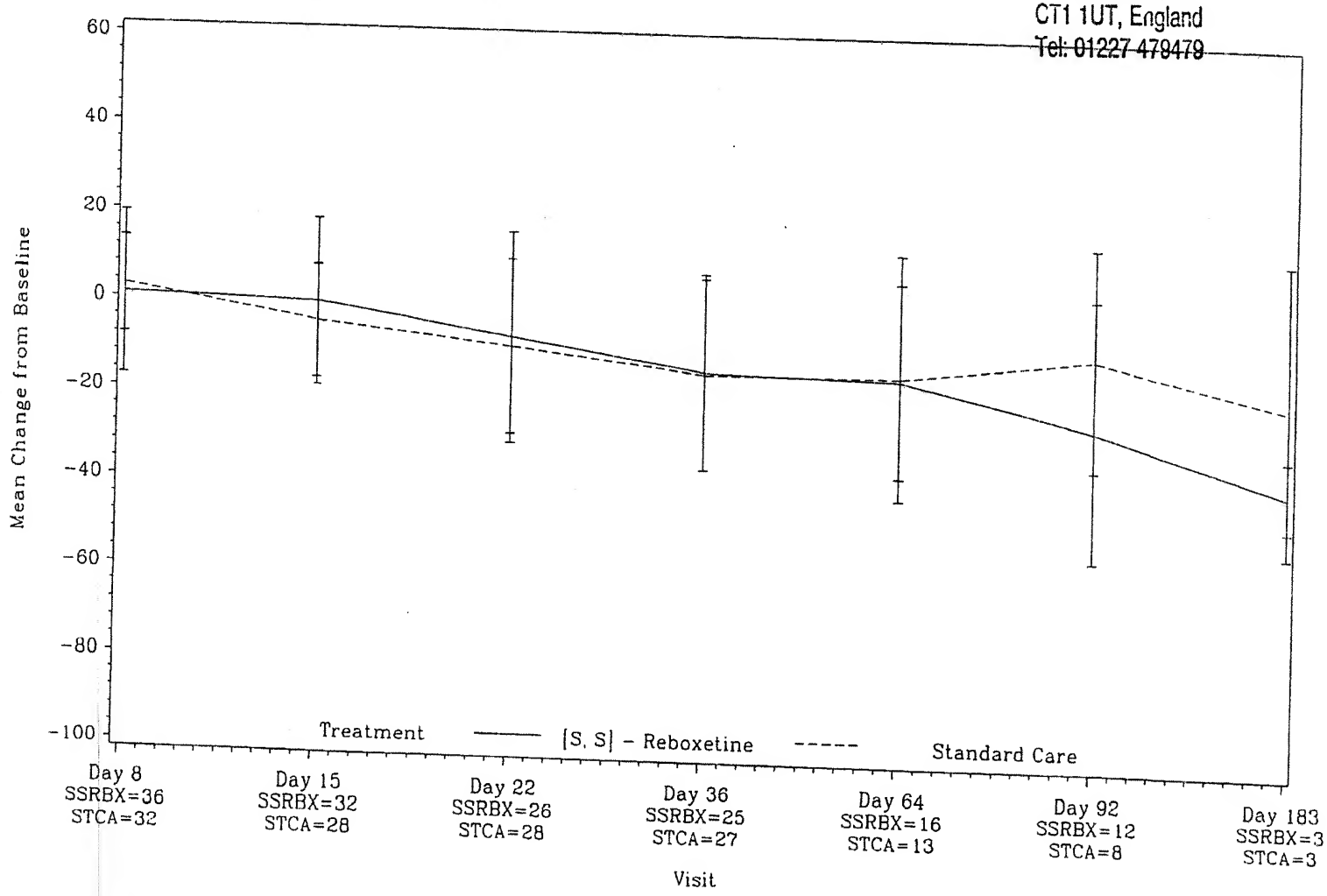
Study ID Numbers: A6061031
Last Updated: June 4, 2007
Record first received: July 4, 2006
ClinicalTrials.gov Identifier: NCT00348894
Health Authority: United States: Food and Drug Administration
ClinicalTrials.gov processed this record on June 08, 2007

U.S. National Library of Medicine, Contact NLM Customer Service
National Institutes of Health, Department of Health & Human Services, USA.gov
Copyright, Privacy, Accessibility, Freedom of Information Act

APPENDIX 3

Andrew Martin Johnson B.A.
NOTARY PUBLIC
20 St. George's Place
Canterbury
CT1 1UT, England
Tel: 01227 479479

SS-reboxetine (enantiomer) Protocol A6061031
Mean (+/- SEM) Change from Baseline in VAS by Visit



Data cut-off date 1st April 2007
SSRBX and STCA denote the number of subjects with VAS scores at the visit for [S, S] - Reboxetine and Standard Care respectively
PFIZER CONFIDENTIAL Date of Reporting Dataset Creation: 30MAY2007 Date of Table Generation: 14JUN2007 (12:44)